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Randomised clinical trial: otilonium bromide improves frequency of abdominal pain, severity of distention and time to relapse in patients with irritable bowel syndrome

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SUMMARY

Background
Otilonium bromide (OB) is a spasmolytic agent that blocks L-Type Calcium channels in human colonic smooth muscle.

Aim
To study the efficacy of OB in symptom control in irritable bowel syndrome (IBS).

Methods
A total of 356 patients (46.16 ± 19 years, 71% female) with IBS participated in a double-blind, randomised, parallel placebo-controlled phase IV study. OB (40 mg t.d.s.) or placebo was administered for 15 weeks, and follow-up was extended 10 additional weeks.

Results
Otilonium bromide (n = 179) and placebo (n = 177) groups had comparable demographics, symptom severity and IBS subtype. Both OB and placebo reduced abdominal pain and IBS symptoms. The effect of OB was significantly greater than placebo in the reduction of weekly frequency of episodes of abdominal pain at the end of treatment period (primary endpoint, −0.90 ± 0.88 vs. −0.65 ± 0.91, P = 0.03), reduction of abdominal bloating (−1.2 ± 1.2 vs. −0.9 ± 1.1, P = 0.02) and global efficacy by patient assessment (1.3 ± 1.1 vs. 1.0 ± 1.1, P = 0.047). Intensity of abdominal pain, proportion of patient responders, safety and quality of life scores were similarly affected by OB and placebo. During follow-up, the therapeutic effect of OB remained greater than placebo in terms of withdrawal rate due to symptom relapse (10% vs. 27%, P = 0.009), global efficacy of treatment and relapse-free probability (P = 0.038).

Conclusions
This placebo-controlled double-blind study shows that otilonium bromide is safe, well tolerated and superior to placebo in reducing the frequency of abdominal pain, severity of abdominal bloating and protecting from symptom relapse in IBS. These results further confirm that patients with IBS can improve during and following treatment with otilonium bromide.

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INTRODUCTION

There is no consensus on the treatment of patients with irritable bowel syndrome (IBS). IBS is a functional bowel disorder clinically characterised by abdominal pain or discomfort accompanied by a change in bowel habits.[1] IBS is a long-lasting recurrent disorder with a strong impact upon patient's health, lifestyle, quality of life and health care utilisation. The diagnosis of IBS should be made on symptoms-based criteria without the need of invasive investigations unless alarm symptoms are present.[2] The Rome process provided the clinical criteria to identify the symptom clusters of this functional gastrointestinal disorder.[1] Recent studies found Rome II and Rome III definitions for IBS that are in high agreement and behave similarly over time concluding that studies that used Rome II subtype criteria and studies that will use Rome III criteria will define comparable populations.[3] Epidemiological studies using these clinical criteria found that the overall prevalence of IBS across Europe is 12%, two-third of the patients are women, most of them had current symptoms, two-third had an 'alternating' IBS subtype and 40% of them had been diagnosed for 10 years or more.[4]

Increased pain sensitivity and altered small bowel and colon motility are the main factors contributing to IBS symptoms. In comparison to healthy controls, IBS patients demonstrate both visceral hypersensitivity and hyperreactive motility.[5] These appear to be independent pathophysiological mechanisms because recent studies found no correlation between hypersensitivity and motor hyperreactivity, and both showed different relationships to the symptoms of IBS.[6] Pain thresholds (visceral hypersensitivity) are closely associated with the intensity of abdominal pain, whereas impaired colonic motility (hypercontractility, hyperreactivity and increased tone) is more strongly associated with abdominal distension and symptoms related with bowel movements.[6] This apparent independence of pain hypersensitivity and impaired motility suggest that different aetiologies – genetic, inflammatory, psychosocial or other factors – are likely to underlie impaired motility and increased pain sensitivity, and different treatments or management strategies may be required for each pathophysiological mechanism.[6] The pharmacological treatment of IBS is symptomatic, and antispasmodics are frequently used to improve IBS symptoms, particularly abdominal pain and bloating.[7] Antispasmodics are believed to reduce pain associated with IBS through inhibition of contractile pathways in the gut wall and improve bowel habits by increasing colonic transit time and therefore reduce stool frequency.[7, 8] Currently available antispasmodics can be classified into three major subclasses: (i) antimuscarinics, (ii) smooth muscle relaxants, and (iii) calcium channel blockers.

Among antispasmodics, otilonium bromide (OB) – a quaternary ammonium derivative compound – has shown consistent evidence of efficacy on IBS patients.[9, 10] Recently, OB was shown to inhibit the main patterns of human sigmoid motility *in vitro* (tone of smooth muscle cells, rhythmic phasic contractions induced by the interstitial cells of Cajal and strong contractions induced by stimulation of enteric motor neurons).[11] Clinically, the main effects of OB include a global improvement of IBS symptoms, a reduction in the frequency and severity of abdominal pain and an increase in the pain threshold during sigmoid balloon distention.[12] However, a number of reviews have questioned the therapeutic value of antispasmodics in IBS, because most available trials are old, have a small sample size, are usually not conducted in an international setting and do not meet current requirements for high quality trials in IBS.[8, 13]

Therefore, the aim of the present study was to confirm the efficacy of otilonium bromide in terms of symptom control in patients with IBS in a double-blind, randomised superiority trial vs. placebo that meets current standards in IBS trial design.

MATERIALS AND METHODS

Patients

Patients over the age of 18 years with IBS according to the Rome II definition were enrolled from secondary care centres, from January 2006 to November 2008.

Study design

This was a superiority trial with a randomised, double-blind, parallel group, placebo-controlled design (EudraCT number 2005-001655-38; trial number MeFI/04/OBR-IBS/001 on http://www.menarini.com/clinical_studies/clinical_trial_registry) to evaluate the effect of otilonium bromide in patients with IBS (IBS). In the absence of internationally available approved drugs for the treatment of IBS, identically looking placebo was chosen as a comparator. This study was conducted in 34 centres in eight countries: Spain (seven centres), Romania (eight centres), Greece (three centres), Portugal (two centres), Turkey (two centres), Belgium (three centres), Russia (six centres) and Germany (three centres) in accordance to ICH guidelines and with the principles of the World Medical Association Declaration of Helsinki; and was

consistent with Good Clinical Practice (GPC) regulations issued by the EMEA and following the 'points to consider in IBS' by EMEA.[14] The study was approved by the ethical committee of all participating centres. Following a run-in period of 2 weeks of single-blind placebo treatment, patients were randomised to receive otilonium bromide (otilonium bromide, 40 mg tablets three times daily before meals, Batch N: 73015) or placebo (one tablet before each meal, Batch N: TFE0516) for 15 weeks.

A computer-generated randomisation list in blocks of four, to balance the random allocation to each treatment, had been prepared by the CRO who coordinated the study.

Patients who achieved 'treatment success' at the end of the 15-week treatment period entered a 10-week post-treatment follow-up period without any additional treatment. No rescue medication was provided for this trial. However, use of rescue medication, which was defined as any medication with analgesic properties that was taken by the patient to treat abdominal pain, was recorded and this was used in the assessment of the post-treatment follow-up phase (see below). Compliance was measured by counting used blisters and unused tablets at each study visit.

At the start of the study, informed consent was obtained, and demographical data, medical history, previous and concomitant medication use were collected. Patients underwent a physical examination including blood pressure and ECG, blood and urine collection, urine pregnancy test (in women of child-bearing potential) and for patients aged >50 years sigmoidoscopy or barium enema (if not done during the last 3 years). IBS-QoL was administered and patients were provided with placebo for single-blind treatment and with the patient diary for weekly recording of signs and symptoms of IBS and questions related to health resources used by patients during the study. At visit 2, patients who met all the inclusion criteria were randomised to the 15-week double-blind treatment phase. Patients needed to have at least two episodes of abdominal pain per week during the 2 weeks of run-in evaluation to be eligible for the trial. At visit 2 and at follow-up visits after 5, 10 and 15 weeks, IBS-QoL was administered and global efficacy assessment of the treatment on IBS symptoms was done by Investigator and patient. Measurements of vital signs, check of concomitant medications and adverse events were performed, and patients were provided with a patient diary for the following 5 weeks. Any unused medication was collected for the assessment of patient compliance and new medication was dispensed. At visit 5 also a physical examination, ECG recording, blood and urine collection and urine pregnancy test (in women of child-bearing potential) were repeated.

Successfully treated patients entered the follow-up period, during which the patient diary was further filled out. At each follow-up visit, the IBS-QoL was administered and a global efficacy assessment of the treatment on IBS symptoms was done by patient and Investigator.

Measurements

Efficacy measurements. The change in the frequency of abdominal pain from baseline at the end of the 15-week treatment period was adopted as primary endpoint. This variable was assessed using a 4-level rating scale used in previous studies based on the number of pain episodes per week registered in the patient diary: 0 = 0 episode; 1 = 1–3 episodes, 2 = 4–7 episodes, 3 = 8 or more episodes.[9] Secondary endpoints were: (i) patient assessment of global treatment efficacy on IBS symptoms using a 4 point scale (from 0 = no efficacy to 3 = excellent efficacy); (ii) physician assessment of global treatment efficacy on IBS symptoms using the same 4 point scale; (iii) patient assessment of treatment efficacy on individual IBS symptoms (pain intensity, severity of bloating-meteorism, stool consistency, mucus and stool frequency); (iv) quality of life (QoL) using the IBS-QoL questionnaire;[15] (v) weekly, monthly and treatment response rates; and (vi) withdrawal rate due to symptom relapse and relapse-free probability during the post-treatment 10 week follow-up period.

Rates of weekly, monthly and treatment responders were calculated according to an algorithm that integrated the most frequent symptoms [pain frequency, pain intensity (as recorded by the verbal rating scale) and bloating/meteorism/distension] reported in the patient's diary. A weekly responder was defined as a patient whose most frequent symptoms (at least two out of three) were improved in that week by at least one point when compared with baseline (highest score recorded in the first and the second week of the 2 week run-in phase). A monthly responder was defined as a patient who had been a weekly responder for at least 2 of 3 weeks in month 1, and for 2 of 4 weeks in months 2–4. A treatment responder was defined as a patient who had been a monthly responder in each month of the period spanning month 1–4 or 2–4 of treatment.[16] (In the first 3-week period, it was hypothesised that the therapeutic efficacy was stabilising; therefore, for the treatment responder definition, the possibility to exclude the first month has been considered).

Treatment success was defined as a patient who had less than two episodes of abdominal pain per week during the last 2 weeks of treatment period. Relapse was defined as a patient who reported at least two episodes of abdominal pain per week or the use of rescue medication (any medication with analgesic properties taken to alleviate abdominal pain) twice a week for two consecutive weeks during the 10 week follow-up period. After achievement of the endpoint 'relapse', the patient was removed from the study. Time to symptom relapse was measured in weeks, and was defined as the time interval between initiation of follow-up and the first of the two consecutive weeks with at least two episodes of abdominal pain per week, if any.

Tolerability and safety assessments. Any adverse event and adverse drug reactions, laboratory safety assessments and vital signs and ECG were assessed.

Statistical methods

The primary endpoint was the change from baseline to the end of the treatment period in the frequency of abdominal pain expressed on a 4-point scale.[9, 16] Based on previous results,[9, 16] at a significance level of 0.05 (two sided) and assuming a score difference between treatments of 0.3 with S.D of 0.85, a sample size of 134 patients per group would have 80% power to reach significance using a Wilcoxon (Mann–Whitney) rank sum test. Assuming a maximum 20% dropout rate, the total number of patients to be recruited was determined at 336.

Primary efficacy end-point data and quality of life data were analysed using an analysis of covariance model; baseline value was included as covariate, and treatment and centre as factors. In case of early discontinuation or missing data, the last value available after randomisation was considered [Last Observation Carried Forward (LOCF) method]. Secondary efficacy endpoints were analysed using a logistic regression for proportional odds, including the treatment and centre effects. Responder data were analysed using a binary logistic regression model including factors for treatment, centre and any relevant covariates. Relapse rates during follow-up were calculated on the subpopulation of 'successfully treated patients' and were analysed using a Cox proportional Hazard model; Kaplan–Meier curves were provided. Additional variables, such as severity of pain and safety data were analysed descriptively. The Intent-to-treat population (or full analysis set – FAS population) was defined for the main analysis and safety population and per protocol population were also assessed. The level of significance was established at 0.05 (two-sided).

RESULTS

Patient characteristics

A total of 355 patients (71% women, mean age 46.2 ± 14.7 years) with IBS (43% mixed, 26% diarrhoea-predominant and 31% constipation-predominant) were enrolled in the study (Table 1). On average, 10.8 patients were recruited per centre (range 1–31) over a total recruitment period of 122 weeks. Most patients were recruited from specialist care; 16 of the study centres were academic practices and these recruited 132 of the patients.

The patient disposition is shown in Figure 1. Dropouts occurred at different levels of the study, and these were mainly due to patients who were lost to follow-up, withdrawal of consent or perceived lack of efficacy. Of 413 screened patients, 356 patients were randomised, 179 to otilonium bromide and 177 to placebo. Two hundred and ninety-five patients finished the treatment phase, of which 167 with treatment success were eligible for post-treatment follow-up. The follow-up phase was completed by 125 patients.

Both treatment groups had comparable demographics and baseline characteristics. About one-fourth of the patients had a history of at least one previous disease other than IBS, of which the most common were infections (6%), depression (4%) and gastrointestinal disorders (4%). About half of the patients had at least one concomitant disease and were taking concomitant treatment, mainly for vascular disorders (17%) (especially hypertension, 14%); immune disorders (10%) (especially drug hypersensitivity, 7%); other gastrointestinal disorders (9%) (especially gastroesophageal reflux disease, 3%, haemorrhoids, 2% and hiatus hernia, 2%); metabolism and nutrition disorders (9%; mainly dyslipidemia, 3%, and hypercholesterolemia, 5%); and miscellaneous musculoskeletal and connective tissue disorders (9%). Mean compliance with study medication was high in both treatment groups at all visits, ranging from 95 to 96%.

Efficacy

Primary endpoint. The primary endpoint, decrease in the frequency of abdominal pain at 15 weeks, was significantly larger in the OB group compared with the placebo group (−0.90 ± 0.88 vs. −0.65 ± 0.91 $P = 0.038$, FAS population). Improvement in frequency of abdominal pain was seen for both arms, with a

Table 1 | Demographical and baseline features (safety population)

Feature	OB (n = 178)	Placebo (n = 177)
Demographical features		
Age (years)	46.4 ± 14.1	46.0 ± 15.3
Elderly (≥65 years)	14 (8%)*	26 (15%)
Sex – females	129 (73%)	123 (70%)
Weight (kg)	68.8 ± 13.3	70.1 ± 15.5
Smoker status		
Nonsmoker	126 (71%)	129 (73%)
Ex smoker	21 (12%)	23 (13%)
Smoker	31 (17%)	25 (14%)
Alcohol		
Nondrinker	135 (76%)	131 (74%)
Average consumption	43 (24%)	46 (26%)
Medical history		
IBS type		
Diarrhoea predominant	46 (26%)	45 (25%)
Constipation-predominant	52 (29%)	58 (33%)
Mixed type	80 (45%)	74 (42%)
Symptoms		
Pain relieved by defecation	165 (93%)	160 (90%)
Change in consistency of stools	167 (94%)	158 (89%)
Change in frequency of stools	164 (92%)	167 (94%)
Patients with a history of at least one disease	41 (23%)	44 (25%)
Patients with at least one concomitant disease	98 (55%)	89 (50%)
Patients with at least one previous treatment	30 (17%)	22 (12%)
Patients with at least one concomitant treatment	98 (55%)	94 (53%)
Baseline symptom severity		
Frequency of abdominal pain	1.86 ± 0.64	1.71 ± 0.67
Severity of abdominal bloating	2.28 ± 0.89	2.31 ± 0.81
Severity of abdominal pain	2.30 ± 0.66	2.37 ± 0.67
Number of stools	2.06 ± 1.74	1.92 ± 1.42
Quality of life	60.15 ± 18.49	58.35 ± 19.14
Baseline stool consistency		
Normal	33 (20%)	37 (22%)
Loose	67 (40%)	51 (30%)
Both loose and hard	1 (1%)	1 (1%)
Hard	68 (40%)	80 (47%)

Categorical variables are expressed in number and percentage and continuous variables are expressed as mean ± s.d.

*P < 0.05 vs. placebo group.

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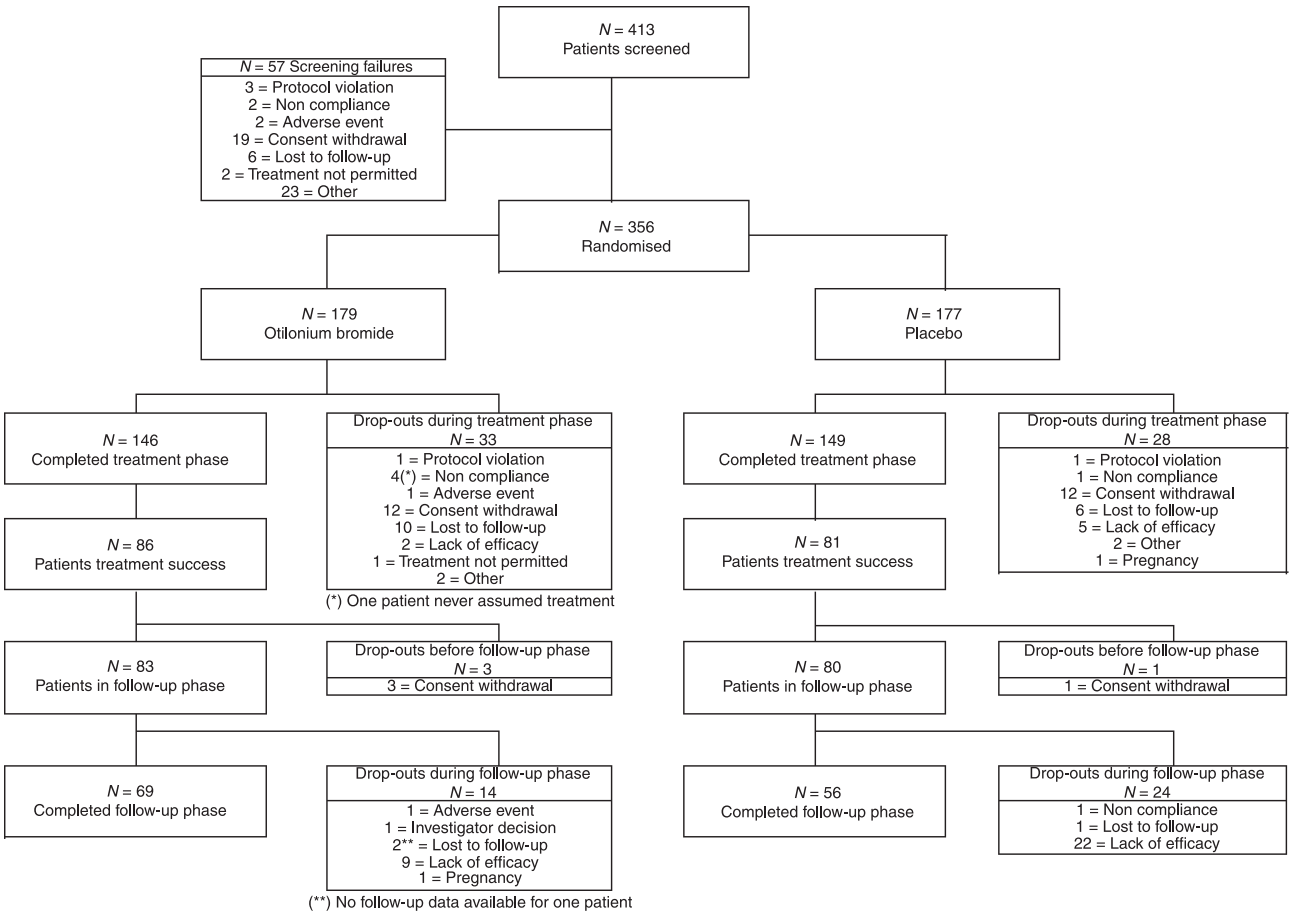

Figure 1 | Trial flow chart.

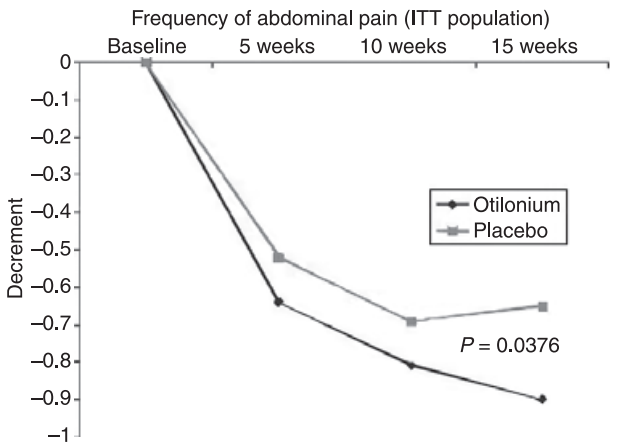

Figure 2 | Primary endpoint: decrement of the score for the frequency of abdominal pain from baseline at 5, 10 and 15 weeks (end of treatment) for OB and placebo in the ITT population.

favourable trend in the OB group in comparison to placebo at all visits, reaching statistical significance at the end of the treatment period (Figure 2). The results were confirmed in the PP population. In addition, the OB group showed a higher number of patients who improved their pain-frequency score by at least 1 point at the end of treatment in comparison to placebo group (117/169 vs. 96/170; $P = 0.018$). Analysis per IBS subgroup did not reveal major differences in response rates to OB between IBS-mixed, IBS-C and IBS-D. Similarly, exploratory analysis of other patient characteristics did not identify a subgroup with a substantially different treatment response.

Secondary endpoints. (i) Symptom severity. Irritable bowel syndrome symptoms (pain intensity, intensity of bloating, stool consistency, presence of mucus) were significantly improved by treatment in both treatment

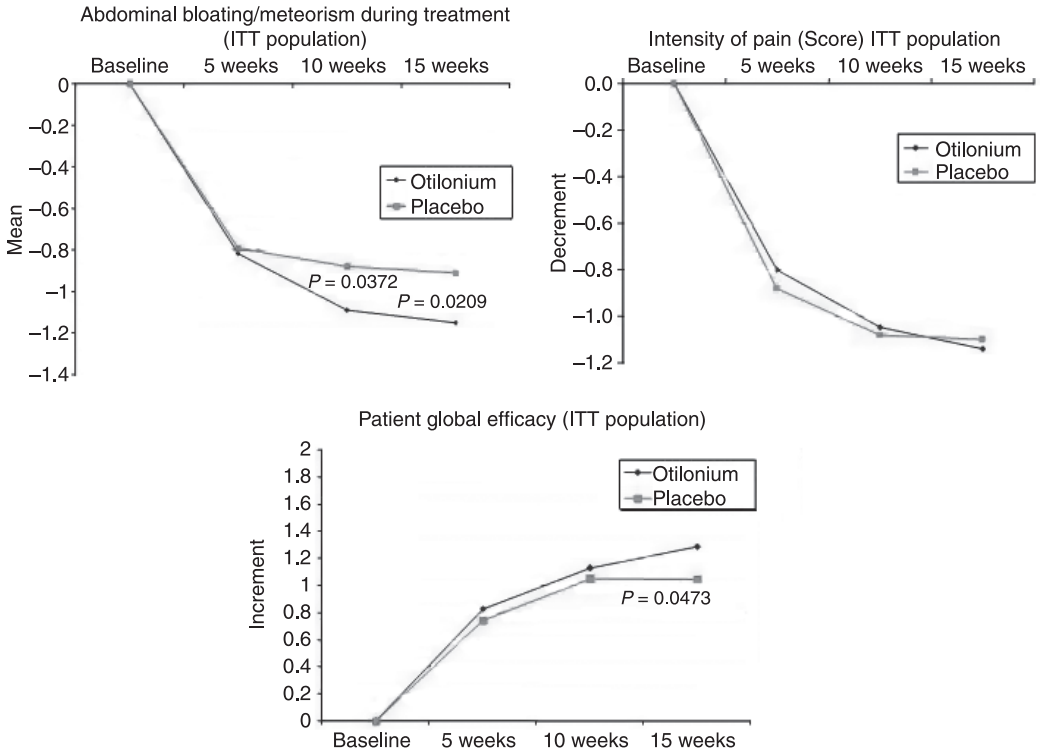

Figure 3 | Secondary endpoints. Changes in the score for intensity of abdominal bloating, intensity of pain and patient global efficacy during treatment (ITT population).

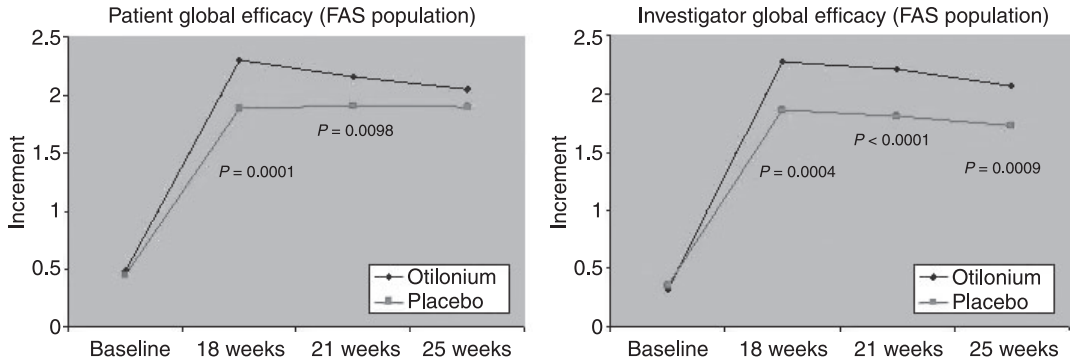

Figure 4 | Follow-up. Global efficacy of treatment according to patient and investigator evaluation.

groups starting from week 5 (all $P < 0.0001$) and the improvement persisted until the end of treatment. The severity of abdominal bloating was significantly improved with OB from week 10 (OB -1.1 ± 1.1 vs. placebo -0.9 ± 1.1 $P = 0.03$) and week 15 (OB-1.2 $\pm$ 1.2 vs. placebo -0.9 ± 1.1 $P = 0.02$) compared with placebo (Figure 3). The average number of stools improved significantly vs. baseline only in the OB group at the end of treatment ($P = 0.004$). No significant differences were observed in pain intensity (Figure 4), mucus and consistency of stools (not shown).

(ii) Global efficacy. The global efficacy of treatment according to patients' judgment significantly improved in both treatment groups from week 5 (OB +0.8 $\pm$ 0.9, placebo +0.7 $\pm$ 1.0; both $P < 0.0001$ vs. baseline) to the end of the treatment period (OB +1.3 $\pm$ 1.1 placebo 1.0 $\pm$ 1.1 $P < 0.0001$ vs. baseline). The comparison between groups became significant at the end of the

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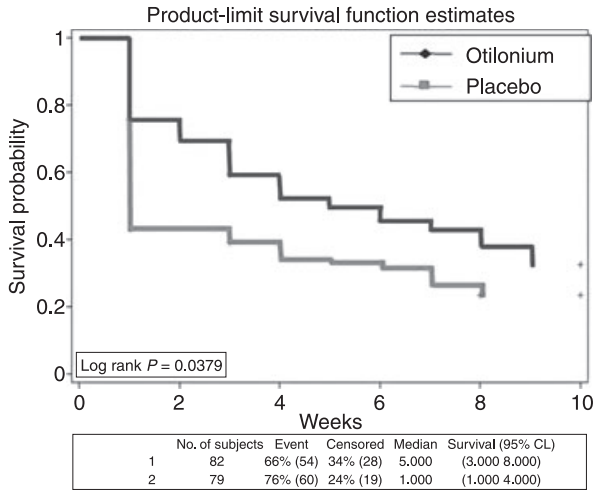

Figure 5 | Effect of treatment with otilonium bromide on time from the end of treatment to symptom relapse.

treatment period in favour of the OB group ($P = 0.047$, Figure 3). Also, according to the investigator, the global efficacy of treatment improved significantly in both treatment groups starting at 5 weeks (OB +0.9 ± 0.9, placebo +0.8 ± 1.0 both $P < 0.0001$ vs. baseline) and persisted until the end of the treatment period (OB +1.3 ± 1.1 placebo 1.1 ± 1.1 $P < 0.0001$ vs. baseline). Statistically significant differences in global efficacy evaluation according to the investigator were not reached.

(iii) Response rates. The weekly response rates were similar in the two treatment groups throughout the study. At the end of treatment, the weekly response rates (73% vs. 73%, N.S.), monthly response rates (83% vs. 83%, N.S.) and treatment success rates (60% vs. 55%, N.S.) did not differ between the OB group and the placebo group.

(iv) Quality of life. Irritable bowel syndrome quality of life raw scores were transformed to a 0–100 scale. The quality of life improvement was similar in the two treatment groups throughout the study. At the end of treatment, the mean change was 15.1 ± 18.4 in the OB group and −15.8 ± 19.1 in the placebo group ($P = 0.95$).

(v) Follow-up of successfully treated patients. A total of 162 patients (82 in OB group and 80 in placebo group) were eligible for the follow-up analysis at the end of double-blind period (Figure 1). During the follow-up period, the withdrawal rate due to symptom relapse was significantly higher in the placebo group compared with OB group (27% vs. 10% $P = 0.0089$) indicating the loss of the therapeutic effect of placebo. According to the patients, the global efficacy of OB was significantly better than placebo at week 18 ($P = 0.0001$) and 21 ($P = 0.009$), and tended to be better than placebo at week 25 ($P = 0.06$). According to the investigators, the global efficacy of OB was significantly better than that of placebo throughout the whole follow-up period (week 18 $P = 0.0004$, week 21 $P < 0.0001$) and week 25 ($P = 0.0009$) (Figure 4). Considering the overall follow-up period, the probability of being relapse-free was significantly higher in the OB group ($P = 0.038$). Figure 5 shows the Kaplan–Meyer curves by treatment group during the follow-up period.

Safety and tolerability

No serious adverse events were reported during the whole study period. A total of 43 patients (24%) in the OB group and of 30 patients (17%) in the placebo group reported at least one adverse event. The most common treatment-emergent adverse events were gastrointestinal events (abdominal pain, flatulence, worsening IBS) and infections, and nearly all were mild to moderate (99% in the OB group and 98% in the placebo group) and were considered unrelated to study treatment (92% in the OB group and 94% in the placebo group). During the treatment period, only three events in the OB group (two cases of dry mouth and one case of nausea) and none in the placebo group were judged related to the treatment by the Investigator. Only one patient in each group was withdrawn because of safety reasons.

DISCUSSION

The present study showed that OB is safe, well tolerated and superior to placebo in reduction of frequency of abdominal pain, severity of abdominal bloating and protecting from symptom relapse in patients with IBS. OB, a musculotropic spasmolytic agent, is believed to reduce pain associated with IBS through inhibition of gut motility.[7, 8, 11, 17]

Otilonium bromide is a quaternary ammonium derivative with poor systemic absorption after oral administration. Pharmacokinetic studies in man found that OB was mainly eliminated by faeces (98%) and minimally excreted in the urine (1%).[18] In animals, OB was shown to accumulate in colonic circular muscle.[19] Accordingly, OB might act at the level of the gastrointestinal tract without systemic absorption. The pathophysiology underlying IBS symptoms is heterogeneous, and both visceral hypersensitivity and altered colonic motility (hypercontractility, hyperreactivity and increased tone) have been implicated in symptom generation.[6, 20] Mechanistic studies have shown the ability of OB to inhibit human sigmoid contractility *in vitro* and *in vivo*, and to

decrease sensitivity to colonic distention.[11, 12, 21, 22] These properties of OB are likely to underlie the beneficial effect of OB on the frequency of abdominal pain and the intensity of abdominal bloating.

The efficacy of OB in providing relief of IBS symptoms has been addressed in four previous trials, which confirmed superior efficacy [symptoms persisted in 111 of 216 (51%) patients in the OB arms compared with 155 of 219 (71%) of those receiving placebo].[7] However, these trials were often limited in sample size, did not recruit internationally and did not use the currently supported endpoints. The present study not only confirmed clinical efficacy in a state-of-the-art international trial but also demonstrated that the reduction of abdominal pain episodes achieved at the end of treatment phase is maintained for a longer period of time during follow-up in patients treated with OB compared with patients treated with placebo. This was associated with a significantly higher withdrawal rate due to symptom relapse in the follow-up period in the placebo group, and a significantly higher probability of being symptom-free in the OB treated group in the overall follow-up. Due to its lipophylic properties, OB's affinity for colonic smooth muscle may extend beyond the treatment period, and this could explain the prolonged efficacy after cessation of drug intake. From a clinical point of view, this long-lasting effect on symptoms is likely to facilitate long-term management of IBS symptoms, especially when intermittent treatment periods are considered.

The primary endpoint of the study was improvement in frequency of abdominal pain over baseline, at the end of the 15-week treatment period. At this time point, a significantly larger therapeutic effect was seen with OB compared with placebo. For the secondary endpoint of severity of abdominal bloating, OB was superior to placebo at weeks 10 and 15. None of the endpoints showed a statistically significant difference at week 5, and this is surprising, as earlier studies suggest a rapid onset of treatment efficacy with OB.[9, 12, 16] Two factors could contribute to this somewhat delayed onset of action. As OB is not systemically absorbed, data on the human pharmacokinetics of the drug, especially at its target of intestinal smooth muscle, are limited. In theory, it is possible that the accumulation of OB at its target tissue takes longer than suspected to date. On the other hand, in previous placebo-controlled comparisons, OB was superior to placebo already during the first month of therapy.[9, 16] In the present study, numerically substantial improvement in symptoms was already seen with OB at week 5, but due to a high placebo effect no significant difference over placebo is seen.

A placebo effect of considerable magnitude is observed in all therapeutic trials in IBS.[23] This has been interpreted as a combination of the natural history of IBS with cyclical variation of symptom intensity over time (entry criteria select patients with active IBS symptoms) and a placebo analgesic effect, possibly mediated through the endogenous opiate system.[24] Attempts to identify predictors of placebo response in IBS have found that the placebo response rate is enhanced by the duration of the study, the number of follow-up visits and the number of patients included in the study.[23] The design of the present study attempted to limit the magnitude of the placebo effect through the use of a single-blind placebo run-in period, and a relatively long interval of 5 weeks between study visits. Nevertheless, the placebo effect remained high and the proportion of weekly, monthly and treatment responders was considerably higher in the present study compared with previous studies with OB in IBS.[9, 16] We do not have a clear explanation for the persistent high placebo response in spite of these measures. Differences in the patient population, the supportive effect of being entered into a long-term trial, patient expectation as well as the patient-practitioner relationship are potential contributing factors. On the other hand, the differences observed between OB and placebo during the follow-up period after cessation of therapy confirm a major effect of OB over placebo in providing symptom relief.

Strengths of the study are its large scale, its multi-centre, international setting and its rigorous placebo-controlled design. The current study also has a number of limitations. First of all, due to the long duration of the study, including the single-blind placebo run-in, only patients with longer-standing, stable IBS symptoms were eligible for the study. The findings of the study therefore are not applicable to patients with more transient IBS symptoms. The primary endpoint, decrease in the frequency of abdominal pain episodes, differs from the binary endpoints used in many recent IBS trials, and this makes it more difficult to compare results to other studies. At baseline, the frequency of abdominal pain ratings showed that patient experienced on average abdominal pain episodes on more than half of the days. At the end of the 15-week period of OB treatment, the incidence decreased to on average less than one episode per week, whereas in the placebo-treated group on average 1–3 episodes of abdominal pain persisted. The severity of abdominal bloating at baseline was of moderate intensity,

and decreased to mild intensity during treatment. Hence, these symptom improvements observed in the present study are of clinically relevant magnitude.

In conclusion, this study shows otilonium bromide is safe, well tolerated and superior to placebo in reducing the frequency of abdominal pain, severity of abdominal bloating and protecting from symptom relapse in patients with IBS. Moreover, patients and investigators' assessments of global efficacy are also significantly superior in patients treated with OB. We also found a very strong effect of placebo during treatment phase as intensity of abdominal pain, proportion of patient responders, quality of life scores and safety measurements were similarly affected by both OB and placebo. Our results further confirm that patients with IBS can improve during and following treatment with otilonium bromide and suggest the possibility to introduce a cyclic therapy for the treatment of this condition – maybe in association with a pure analgesic drug – with maintenance of the positive effects of the drug during suspension periods.

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